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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,905	10/05/2005	Oliver Schadt	MERCK-3075	6249

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EXAMINER	
JARRELL, NOBLE E	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
03/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,905	SCHADT ET AL.	
	Examiner	Art Unit	
	NOBLE JARRELL	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9,11 and 13-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9,11 and 13-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/14/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. The 35 U.S.C. 112 1st and 2nd paragraph rejections has been overcome by the amendment filed 11/10/2008.

2. The rejection under 35 U.S.C 102 and 103 have been overcome by the amendment filed 11/10/2008.

3. The double patenting rejections regarding applications 10/552065 and 10/552064 have been overcome by the terminal disclaimer filed 22 May 2008, which was approved.

Information Disclosure Statement

4. The information disclosure statement filed 1/14/2009 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. It has been placed in the application file, but the information referred to therein has not been considered. The relevance of document B10 is difficult to determine because it is published in Japanese.

5. The information disclosure statement filed 1/14/2009 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. Document C13 has not been submitted and therefore has not been considered.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 11, 13-16, and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *in vitro* inhibition of 5-HT_{2A} receptors, does not reasonably provide enablement for treatment or prevention of sleeping disorders and schzophrenia and the prevention of premenstrual syndrome. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to the treatment of disorders related to modulation of 5-HT_{2A} receptors using compounds composed of pyrazole ring bonded to a phenyl or pyridine ring through the 1-position of the pyrazole ring. In the same compound, the 5-position of pyrazole ring is modified with a $(CH_2)_{0-6}$phenyl moiety or a $(CH_2)_{0-6}$heterocycle moiety Thus, the claims taken together with the

specification imply that these compounds can treat disorders related to 5-HT_{2A} receptor modulation.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Roth et al. (*Expert Opinion in Therapeutic Targets*, **2001**, *5(6)*, 685-95) teach that 5-$HT_{2A/2c}$ antagonism may be linked to treatment of sleeping disorders (section 3.3, paragraph 1, page 690). This teaching suggests that future research is needed to determine if 5-$HT_{2A/2c}$ antagonism is really linked to *in vivo* treatment of diseases. The conclusion states that the 5-$HT_{2A/2c}$ receptor may be a potential avenue of treatment for a large number of common diseases including depression, anxiety, schizophrenia, OCD, and obesity. This teaching suggests that future research is needed to determine if the 5-$HT_{2A/2c}$ receptor is a viable *in vivo* target.

Premenstrual syndrome is not curable (is not responsive to prophylaxis) ("Premenstrual Syndrome", http://www.medicinenet.com/premenstrual_syndrome/page5.html, accessed 19 September 2007, cited in previous office action).

(5) The relative skill of those in the art:

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in treatment of disorders related to 5-$HT_{2A/2C}$ receptors.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for *in vitro* inhibition of 5-HT_{2A} receptors.

However, the specification does not provide guidance for treatment or prevention of sleeping disorders and schizophrenia and the prevention of premenstrual syndrome.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed by the references above, particularly with regards to claims 11, 13-16, and 18 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-9, 11, 13-16, and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims are unclear because the definition of variable "het" in claim 1 is unclear. The definition provided in claim 1 is "a saturated, unsaturated, or aromatic mono- or bicyclic heterocyclic organic radical containing one or more hetero atoms". Although the definition is understood to be a heterocyclic ring, it is now unclear as to what heterocyclic rings applicants mean to include in this definition. The size of the ring can be anywhere from 3 atoms and up, and include any number of heteroatoms. This variable has to be clear because the core structure of formula I is small (the only required portion is a phenyl or pyridine ring bonded to the 1-position of a pyrazole ring. The variable "het" is present in variables R^1, R^3, and R^6, and depending on what the ring is, it can control classification. For example, if "het" is azepane, the controlling class is class 540, subclass 484.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

11. Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Rainer (US 4325962, issued 20 April 1982). Rainer teaches a compound (the final product of example 19, column 16, lines 40-63). In the specified compound, instant variables of formula I are defined as follows: R^1 is CH_2CO_2H; R^2 is methyl; R^3 is phenyl; X is CH, and R^6 is phenyl. Pharmaceutical compositions comprising this compound are taught from column 36, line 60 to column 37, line 53.

12. Claims 1-5 are rejected under 35 U.S.C. 102(b) as being anticipated by Rainer (US 4146721, issued 27 March 1979). Rainer teaches the final product of example 19 (column 16, lines 40-63). In this compound, variables of the instant application are defined as follows: R^1 is

methyl; R^2 is CH_2CO_2H; R^3 is phenyl; X is CH; and R^6 is phenyl. Pharmaceutical compositions are taught from column 37, lines 1-65.

13. Claims 1-8 are rejected under 35 U.S.C. 102(e) as being anticipated by Schiemann et al. (WO 03/031435, published 17 April 2003, filed 11 September 2002). Schiemann et al. teach compound 9 (example 5, page 26), compound 10 (example 6, page 27), 11 (example 7, page 27), 22 (example 12, page 30), and 32 (example 17, page 33). In each of these compounds, variable X is N, R^6 is phenyl, and R^3 is *o*-F-phenyl. Variable R^1 is CO_2Et, CH_2OH, CHO, and $(CH_2)_2$-morpholino. In claim 7, compounds of formulae IA, IC, and IE are anticipated by these compounds. Pharmaceutical compositions comprising these compounds are taught from page 23, line 8 to page 24, line 2.

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

16. Claims 1-8 and 17 rejected under 35 U.S.C. 103(a) as being unpatentable over Schiemann et al. (WO 03/031435, published 17 April 2003, filed 11 September 2002).

Determining the scope and contents of the prior art

Schiemann et al. teach compounds 266-280 (pages 49-50), 416-330 (pages 52-53), 366-380 (pages 56-57), 416-430 (pages 59-60), 466-480 (pages 62-63), 516-530 (pages 66-67), 566-580 (pages 69-70), 616-630 (pages 72-73), and 716-730 (pages 79-80). In these compounds, instant variables X and R^2 are always N and H respectively. Instant variable R^6 is selected from the group consisting of phenyl, *p*-CN-phenyl, *p*-F-phenyl, pyridine, and tetrazole. Instant variable R^3 is selected from the group consisting of phenyl, *o*-CN-phenyl, or *o*-CF_3-phenyl. Instant variable R^1 is CO_2Et, CH_2OH, CHO, $(CH_2)_2OH$, CH=N-OMe, CH_2-morpholino, CH_2-piperazine, CH_2-4-methyl-piperazine, or $(CH_2)_2$-morpholino. Pharmaceutical compositions comprising these compounds are taught from page 23, line 8 to page 24, line 2. These compounds are being used as glycine transport inhibitors for the treatment of various diseases (see abstract).

Ascertaining the differences between the prior art and the claims at issue

In instant formula I, the instance of formula I when X is N is a 2-pyridyl ring connected to the 1-position of a pyrazole ring. In compounds taught by Schiemann et al., the core structure is a 3-pyridiyl ring connected to the one-position of pyrazole.

Resolving the level of ordinary skill in the pertinent art

Those of relative skill in the art are those with level of skill of the authors of the references cited to support the examiner's position. The relative skill of those in this art is MD's, PhD's, or those with advanced degrees and the requisite experience in preparation of compounds of the elected group.

Considering objective evidence present in the application indicating obviousness or nonobviousness

The only difference between compounds taught by Schiemann et al. is the point of attachment between the pyridine ring and the pyrazole ring. In the instant application, the point of attachment is the 2-position, and in Schiemann et al. the point of attachment is the 3-position. Even though compounds of Schiemann et al. are not being used in the same disorders as the instant application, it is obvious to try these compounds because the only structural difference is the point of attachment between the pyridine ring with variable X and the pyrazole ring. Claim 17 is rendered obvious because the 4-ethyl-piperazine is an analogue of a 4-methyl-piperazine ring.

Sterling Drug Inc. v. Watson, Comr. Pats. (108 USPQ 37) teaches that the test to be applied in matter of the patentability of a compound that is a homologue of another is whether the beneficial characteristics are both unexpected and obvious. In compounds 616-630 of Schiemann et al., a methyl group is attached to the 4-position of piperazine. In claim 17, an ethyl group attached to the 4-position of a piperazine ring. Because these two groups only differ by CH_2, they are considered analogous to one another. Thus, a compound of claim 17 when variable "het" is 4-ethyl-piperazine is rendered obvious.

Conclusion

17. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NOBLE JARRELL whose telephone number is (571)272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/
Examiner, Art Unit 1624

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Primary Examiner, Art Unit 1624
For James Wilson, SPE Art Unit 1624